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NEONATAL CAPSAICIN TREATMENT BLOCKS FEEDING SUPPRESSION ELICITED BY SYSTEMICALLY BUT NOT CENTRALLY ADMINISTERED BOMBESIN. Z. Merali, D. Michaud. School of Psychology and Dept. of Pharmacology, University of Ottawa, Canada.

Capsaicin, a neurotoxin commonly found in chili peppers, has been shown to permanently degenerate some of the afferent neurons in neonatal rats. It is of interest that capsaicin treated rats display increased grooming and scratching behaviors like those seen following central injection of bombesin (BN). The purpose of this study was to determine whether neonatal capsaicin treatment altered response to BN in adulthood. On day two of life, capsaicin (50 mg/kg; s.c.) was administered to neonatal rats (n=20). The control group (n=20) received the same volume of vehicle. The weight gain was significantly lower in capsaicin-treated animals starting day 28 and this effect was independent of their activity level. The frequencies of scratching and grooming behaviors were significantly increased in the capsaicin group from day 21 to 42. Next we tested the response of both groups to systemically injected BN. Rats food deprived for 18 h were injected with various doses of BN (0, 4, 8, and 16 mg/kg; i.p.) in randomized order, and given access to food for a 4 h. A dose- and time-dependent suppression of food intake was observed in controls. However, BN failed to suppress food intake in capsaicin-treated animals. We next explored whether the response to centrally administered BN was also affected. Both controls (n=6) and capsaicin treated (n=6) groups responded to central BN (0, 0.1, 0.25, 0.5 mg; i.c.v.) in a dose- and time-dependent manner, and there were no significant group differences in terms of the satiety response. Thus the central efferent system mediating satiety effects of BN did not seem to be affected by neonatal capsaicin exposure. There are several controversial theories about whether systemic BN elicits its effects by endocrine, paracrine, or neural mechanisms. Our study clearly supports the notion that systemic BN mediates it's effects neuronally, through the capsaicin-sensitive myelinated A-delta and/or unmyelinated C-fibers of the primary afferent fibers.

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INHIBITION OF CRF-INDUCED CARDIOVASCULAR AND ENDOCRINE RESPONSES *IN VIVO* AND *IN VITRO* BY CP-154,526, A NOVEL NONPEPTIDE CRF RECEPTOR ANTAGONIST. R.M. Richter, M.J. Mulvany. Institute of Molecular Pharmacology, 10315 Berlin, Germany and Department of Pharmacology, Aarhus University, 8000 Aarhus C., Denmark.

Corticotropin-releasing factor (CRF), a 41-amino acid hypothalamic peptide, plays a critical role in activating the hypothalamo-pituitary-adrenal (HPA) axis by controlling the release of ACTH from the anterior pituitary and may act as a neurotransmitter in both brain and periphery. CRF evokes prominent stress responses as well as marked cardiovascular effects. With the recognition that CRF also plays a role in the pathophysiology of various stress-related disorders, CRF antagonists may have therapeutic application. Recently, a novel nonpeptide CRF receptor antagonist, CP-154,526 (butyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine. Pfizer), was developed.

In the present study we evaluated the antagonist potency of CP-154,526 in blocking central and peripheral mediated effects of CRF in five different bioassays *in vivo* and *in vitro*. The novel antagonist blocked in a dose-dependent (0.4 to 10 mg/kg, iv) and sustained fashion ($\approx$ 1 hour) centrally evoked (1 µg CRF, icv) cardiovascular responses (MAP and HR) in conscious rats. The ID_{50} was about 0.4 mg/kg for MAP and 0.8 mg/kg CP-154,526 for HR, respectively. In parallel, the CRF-induced increase in plasma ACTH and corticosterone levels was significantly attenuated after pretreatment with CP-154,526 (2 mg/kg, iv) (ACTH: by 80%, corticosterone: by 60% of the peak value).

In contrast, the ability of CP-154,526 (1 to 5 mg/kg, iv) to antagonize peripherally mediated cardiovascular responses (thought to be mediated through CRF_2-receptors) was weak, even with 50 µg/kg CRF, iv. Also, the ability of CP-154,526 to block the CRF-induced relaxation (1 to 100 nM; $EC_{50} \approx$ 10 nM) of pre-contracted rat mesenteric small arteries *in vitro* was low. Here CP-154,526 caused a marked shift in the concentration-relaxation curve only at a concentration of 3×10^{-6} M.

The results suggest that the nonpetide CRF receptor antagonist CP-154,526 blocks selectively biological activities mediated by the CRF_1 receptor identified in brain and pituitary.